An Advisory Committee Review
National Advisory Committee on Immunization (NACI)

NACI Literature Review on the Comparative Effectiveness and Immunogenicity of Subunit and Split Virus Inactivated Influenza Vaccines in Adults 65 Years of Age and Older

Public Health Agency of Canada | Agence de la santé publique du Canada

Canada

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization. PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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EXECUTIVE SUMMARY

Subunit and split virus inactivated influenza vaccines are two commonly used types of seasonal influenza vaccines, and continue to dominate the market in Canada. Although these two formulations of influenza vaccine have been available for many decades, NACI has not previously conducted a literature review to investigate the comparative vaccine effectiveness of these different formulations. A difference in vaccine effectiveness between these formulations would be especially important for older adults (65 years of age or older), since there is evidence that older adults experience more severe illness due to influenza and have reduced vaccine effectiveness compared to younger adults. To address this gap, NACI conducted a literature review to examine the vaccine effectiveness and immunogenicity of unadjuvanted, standard dose subunit inactivated influenza vaccines compared to unadjuvanted, standard dose split virus inactivated influenza vaccines in adults 65 years of age and older. Eight studies were identified which assessed either the vaccine effectiveness or immunogenicity of subunit compared with split virus inactivated influenza vaccines. Included studies did not show statistically significant differences in vaccine effectiveness or immunogenicity. Methodological limitations and/or study quality was a concern for all included studies. NACI concludes that there is insufficient evidence to determine the comparative vaccine effectiveness and immunogenicity of unadjuvanted subunit and split virus inactivated influenza vaccines in adults 65 years of age and older (Grade I Evidence). The evidence is not sufficient to support specific recommendations on the differential use of subunit and split virus inactivated influenza vaccines in older adults.

I. INTRODUCTION

Background

Many different technologies are currently used in the formulation of influenza vaccines. The split virus and subunit vaccines, both consisting of disrupted virus particles, were some of the first technologies derived following early inactivated whole virus vaccines, which were developed in the 1940s[1]. Split virus vaccines contain whole inactivated viruses split with detergent, ether, or both, while subunit vaccines are made of purified hemagglutinin (HA) and neuraminidase.

Newer technologies and formulations for influenza vaccines have since been introduced, such as higher doses of antigen or combining the antigen with newer adjuvants. However, standard dose subunit and split virus inactivated influenza vaccines (IIVs) are still the most commonly used seasonal influenza vaccines, as these vaccines have well-established safety profiles and are less expensive than newer formulations. Therefore, a large number of the seasonal influenza vaccines available for use in Canada are standard dose subunit or split virus IIVs[2]. A full list of influenza vaccines available in Canada can be found in Appendix D.

NACI has not previously critically appraised the evidence on the comparative vaccine effectiveness (VE) and immunogenicity of subunit versus split virus IIV in any age group. If one of the vaccine types were more effective, it would be important to know this, particularly for older Canadian adults (65 years of age and older), who are at highest risk of influenza-related hospitalizations[3] and deaths[4]. Older adults may also experience reduced VE against influenza infection compared to younger age groups[5].

To inform NACI on potentially important differences between subunit and split virus IIVs in older adults, a literature review was conducted to examine the VE and immunogenicity of subunit and split virus IIVs in adults 65 years of age and older.

The primary objective of this literature review was:

- To compare the VE and immunogenicity of standard dose, unadjuvanted subunit IIV versus standard dose, unadjuvanted split virus IIV in adults 65 years of age and older.

II. METHODS

This literature review's methodology was specified a priori in a written protocol, and was based on rapid review methods developed by Tricco et al.[6]. The NACI Influenza Working Group verified the inclusion and exclusion criteria and the review methods used in this literature review.

II.1 Research question

Does the VE, immunogenicity, or both of unadjuvanted, standard dose subunit IIV differ from unadjuvanted, standard dose split virus IIV among adults 65 years of age and older?

P (population): adults ≥65 years of age
I (intervention): unadjuvanted, standard dose subunit IIV
C (comparison): unadjuvanted, standard dose split virus IIV
O (outcome): VE, immunogenicity, or both

Search strategy

A search strategy was developed in consultation with a federal Reference Librarian (Health Library), and included search terms for subunit influenza vaccine, split virus influenza vaccine, VE, and immunogenicity. The complete search strategy is presented in Appendix A. The search was restricted to studies published in English or French. The final database search was executed on October 13, 2017.

To ensure the timeliness of this review, the literature search was limited to two bibliographic databases (EMBASE and MEDLINE) and one clinical trial database (ClinicalTrials.gov), and the search was limited to studies published in 2007 or later. Searches of the grey literature and hand searches of the reference lists of included articles were not planned.

Identification of eligible studies

Articles retrieved in the search were loaded into RefWorks (ProQuest LLC, Ann Arbor, MI) and duplicate records were removed. Non-duplicate records were then uploaded into DistillerSR (Evidence Partners, Ottawa, Canada) and screened by title and abstract. The full texts for articles that were relevant based on the inclusion and exclusion criteria, or that had insufficient information to exclude, were retrieved and assessed for eligibility through full-text screening.

Studies were included if they met the following criteria:

1. The study directly or indirectly compares the VE or immunogenicity of an unadjuvanted, standard dose subunit IIV to an unadjuvanted, standard dose split virus IIV;
2. The study population is within the age range of interest (≥65 years of age).

Studies were excluded if they met one or more of the following criteria:

1. The study does not present VE or immunogenicity for both vaccine types of interest;
2. The study is in a language other than English or French;

3. The study is a non-human, in vivo, or in vitro study;
4. The article is an editorial, opinion, or news report;
5. The study presents only secondary research.

Screening and eligibility assessment were completed by a single reviewer with no validation.

Data extraction, synthesis, and quality assessment

Data from included studies were extracted into evidence tables, defined a priori. The quality (internal validity) of included studies was assessed using criteria outlined by Harris et al. (2001)[7], which are presented in Appendix C. Data extraction and quality assessment were both completed by one reviewer and verified by a second reviewer. Results from included studies were synthesized narratively.

II.2 Post-hoc modifications

Post-hoc modifications of the search strategy

The study protocol was modified to include a hand search of the reference lists of included articles due to the small number of records retrieved from the initial database search. Because the results of the hand search revealed many pivotal studies that were published prior to 2007, the a priori search criteria were modified by expanding the search to include three additional databases (Cochrane Central Register of Controlled Trials, Scopus, and Web of Science), and removing the publication date restriction.

Post-hoc modifications of the study eligibility criteria

A large proportion of studies identified during the initial eligibility assessment defined older adults as individuals ≥60 years of age but were otherwise eligible[8-12]. Therefore, the eligibility criteria were modified to include studies in which older adult sub-populations were defined as individuals ≥60 years of age.

III. RESULTS

III.1 Overview

The initial database search retrieved 30 records after removal of duplicates; only three of these studies met inclusion criteria. After post-hoc adjustments to the study protocol, 41 unique studies were retrieved from the database search and eight were deemed eligible for inclusion based on the revised eligibility criteria. A PRISMA flow diagram detailing the results from both searches is presented in Appendix B.

III.2 Vaccine Effectiveness

Three of the included studies reported on the VE of unadjuvanted, standard dose subunit and split virus IIVs[12-14], with only one study reporting a direct estimate for the difference in VE between the two types of influenza vaccines[13]. All three studies used test-negative case-control designs and all three were rated as "fair" according to the Harris et al. criteria. The main methodological concern for the Talbot et al. study was the response rate, as only 539 participants had sufficient data for analysis of a total of 840 enrolled participants[13]. The studies by Kissling et al.[12] and Rondy et al.[14] both used data collected through the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) network, which provides VE estimates for seasonal influenza vaccines in Europe. The main concern for these studies was that their adjusted VE estimates did not account for all potentially relevant confounders. Also of note, VE against hospitalization associated with influenza stratified by vaccine type was not included in a

follow-up study conducted by Rondy et al. due to the potential for residual confounding of VE estimates by geographic location. Geographic location would be an important confounder given differences in influenza strain diversity across Europe during the 2016–2017 influenza season and the penchant for many study sites to only offer one vaccine type (author correspondence). Two of the studies were funded through government grants[13, 14] and one was co-funded by pharmaceutical companies, a public health IT company (author-affiliated), and the study sites[12]. A full account of study characteristics and results on VE can be found in Appendix E.

No effectiveness studies were identified that compared quadrivalent inactivated influenza vaccine (QIV) with trivalent inactivated influenza vaccine (TIV) formulations of subunit or split virus IIVs.

Vaccine effectiveness against influenza infection

Talbot et al. reported on the absolute difference in adjusted VE (aVE) against laboratory-confirmed influenza between subunit and split virus IIVs among adults ≥65 years and ≥70 years of age. In these analyses, the absolute difference in aVE against any influenza strain (split virus aVE minus subunit aVE) was 41.9% (95% confidence interval [CI]: -5.5–190.6%) among adults ≥65 years of age and 62.4% (95% CI: -112.4–555.1%) among adults ≥70 years of age. These differences in aVE were not statistically significant and had wide CIs[13]. Of note, the study detected statistically significantly higher aVE for split virus IIV compared to subunit IIV among adults ≥50 years for protection against any strain of laboratory-confirmed influenza and against influenza B specifically; however, these estimates had wide CIs which makes the exact difference in aVE difficult to determine (data not reported here). Although Kissling et al. did not directly compare subunit and split virus VE, the aVE estimates against laboratory-confirmed influenza infection appeared similar (i.e. widely overlapping CIs) for subunit (aVE: 64.6%; 95% CI: 21.6–84.0%) and split virus (aVE: 54.1%; 95% CI: 16.8–74.7%) IIVs among adults ≥60 years of age[12].

Vaccine effectiveness against influenza-associated hospitalization

The study by Rondy et al. reported VE against hospitalization due to laboratory-confirmed influenza[14]. While Rondy et al. did not directly compare subunit and split virus VE, aVE estimates against hospitalized influenza B appeared similar between subunit (aVE: 49.0%; 95% CI: 13.5–70.0%) and split virus (aVE: 54.1%; 95% CI: 18.9–74.0%) IIVs among adults ≥65 years of age. However, while split virus IIV was statistically significantly protective against hospitalization associated with influenza A(H1N1)pdm09 (aVE: 54.7%; 95% CI: 30.7–70.4%), subunit IIV was not (aVE: 28.1%; 95% CI: -8.6–52.4%). The authors noted that the 95% CIs for the VE of subunit and split virus IIVs against influenza A(H1N1)pdm09 were widely overlapping, and that estimates should be interpreted with caution.

III.3 Immunogenicity

Five studies were identified that reported on the immunogenicity of subunit and split virus TIVs [8-11, 15]. Of these, only two reported a direct comparison between the two types of vaccines[8, 11]. The included studies used a range of designs, including two randomized controlled trials (RCTs)[10, 15], one cohort[8], one clinical controlled trial (CCT)[11], and one study for which the design could not be determined due to insufficient reporting[9]. Only one study stated the authors' conflicts of interest and funding sources, which consisted of a research foundation and a government grant, with pharmaceutical companies providing funding only for immunologic testing[15]. The other studies did not discuss funding or conflicts of interest; however, two of the studies' authors were all affiliated with a publicly-owned university[8, 11], another study's authors were all affiliated with a pharmaceutical company[9], and another study's authors were affiliated

with either a medical centre, a diagnostic imaging centre, or a pharmaceutical company[10]. A full account of study characteristics and results on immunogenicity can be found in Appendix F.

Three of the five studies were evaluable by Harris et al. criteria, of which one received a "fair" rating[10] and two received "poor" ratings[8, 11]. For both studies that received a "poor" rating, the major concern was the initial assembly of comparable intervention groups. For the other two studies, neither reported study methodology in sufficient detail to assess study quality[9, 15].

No immunogenicity studies were identified comparing QIV with TIV formulations of subunit and split virus IIVs.

Correlates of protection against influenza infection

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) previously used serological correlates of influenza protection for adults >60 years of age to determine vaccine licensing in the EU[16]. The CHMP revised their guidance in 2017 such that specific thresholds for serological assessments are no longer used[17]. Therefore, the definitions for geometric mean fold rise (GMFR), seroprotection, and seroconversion used in all of the studies on immunogenicity included in this review coincide with the previously reported threshold criteria used by the CHMP.

Protection against influenza vaccine strains

Findings from the two studies that directly compared the immunogenicity of subunit and split virus IIVs were inconsistent[8, 11]. In the study conducted by Camilloni et al., the split virus vaccine conferred statistically significantly lower correlates of protection for influenza A(H1N1) when compared to the subunit vaccine (relative GMFR: $p<0.01$; relative seroprotection rate: $p<0.01$; relative seroconversion rate: $p<0.01$), but conferred a statistically significantly higher rate of seroprotection against influenza B ($p<0.01$)[8]. There was no statistically significant difference in GMFR or seroconversion rate for influenza B, or in GMFR, seroprotection rate, or seroconversion rate for influenza A(H3N2). Results from the second study, conducted by Zei et al., showed that the split virus vaccine had a statistically significantly higher seroprotection rate than the subunit vaccine for influenza A(H1N1) ($p<0.05$), and a statistically significantly higher seroconversion rate for influenza A(H3N2) ($p<0.05$) and B ($p<0.001$)[11]. There was no difference between the seroconversion rates for influenza A(H1N1) or between the seroprotection rates for influenza A(H3N2) or B for the two vaccines. GMFR was not reported in this study.

In the study conducted by Morales et al., the relative correlates of protection were not calculated; instead, the point estimates for subunit and split virus IIVs were given separately[10]. The GMFR for influenza B for the subunit vaccine (4.1; 95% CI: 3.1–5.3) was lower than for the split virus vaccine (9.3; 95% CI: 7.0–12.34). The proportion of participants with at least a four-fold increase in HA titre post-vaccination (first definition of seroconversion used by the authors) appeared similar between the vaccines for influenza A(H1N1) (subunit: 79%, 95% CI: 58–93%; split: 55%, 95% CI: 32–77%), A(H3N2) (subunit: 72%, 95% CI: 59–83%; split: 75%, 95% CI: 63–84%), and B (subunit: 54%, 95% CI: 40–67%; split: 71%, 95% CI: 58–83%). GMFR for influenza A(H1N1) (subunit: 14.4, 95% CI: 10.0–20.7; split: 16.8, 95% CI: 11.5–24.4) and A(H3N2) (subunit: 10.9, 95% CI: 7.6–15.8; split: 10.9, 95% CI: 7.6–15.7) were also similar. Seroprotection rates were only reported as a range and 95% CIs were not provided [subunit (range): 88%–98%; split virus (range): 88%–97%], and only point estimates without 95% CIs were provided for the proportion of participants who had pre-vaccination HA titres ≤1:10 and post-vaccination HA titres ≥1:40 (second definition of seroconversion used by the authors) for

influenza A(H1N1) (subunit: 81%; split virus: 86%), A(H3N2) (subunit: 88%; split virus: 86%), and B (subunit: 67%; split virus: 89%).

Del Giudice et al. also conducted a study that examined seroprotection for A(H3N2) by vaccine type and found that subunit and split virus IIVs had similar point estimates (subunit: 96.5%; split virus: 96.7%) but did not report CIs for these estimates.

Cross-protection against variant influenza strains

Skowronski et al. conducted a study to assess the level of cross-protective antibodies for a novel swine-origin variant of influenza A(H3N2)[15]. The seroprotection rate and seroconversion rate appeared similar between the group that received the subunit vaccine (seroprotection rate: 27%, 95% CI: 17–37%; seroconversion rate: 0%, 95% CI: not reported) and the group that received the split virus vaccine (seroprotection rate: 32%, 95% CI: 15–50%; seroconversion rate: 7%, 95% CI: 0–21%). Only point estimates without 95% CIs for GMFR were reported for both groups (subunit: 1.13; split virus: 1.51).

Del Giudice et al. also conducted a study that assessed the level of cross-protective antibodies for a mismatched influenza A(H3N2) strain[9] and found similar point estimates for seroprotection for both vaccines (subunit: 75.9%; split virus: 80%) but did not report any CIs.

IV. DISCUSSION/SUMMARY

IV.1 Summary of evidence

Three studies were found that assessed the VE of subunit and split virus IIVs[12, 14]. There were no statistically significant differences in VE in adults ≥65 years of age against infection with any influenza virus strain, or against infection with influenza A(H1N1), A(H3N2), or B virus specifically [12, 13]. One study found no difference in VE against hospitalization associated with influenza B between subunit and split virus IIV, but did find that split virus IIV was effective in reducing hospitalization associated with influenza A(H1N1) while subunit IIV was not[14]. These latter estimates, however, had widely overlapping CIs, and the difference in aVE between the two vaccines was not assessed directly, making it difficult to determine if there was a significant difference in aVE between the vaccines. The potentially uncontrolled confounders which limited the assessment of VE by vaccine type in a follow-up study to the one conducted by Rondy et al. (2017) are also likely present in the two multicentre European studies included in this review that were also completed using the I-MOVE network[12, 14]. Therefore, any comparisons between subunit and split virus IIV VE in these studies should be interpreted with caution.

Findings from the studies that reported on immunogenicity were not consistent[8-11, 15]. Of the five included studies, only two directly compared measures of immunogenicity between subunit and split virus IIVs, and these studies did not demonstrate consistent differences in immunogenicity by influenza type or subtype, or by serological assessment (i.e. GMFR, seroprotection rate, or seroconversion rate)[8, 11]. For the studies that did not directly compare subunit and split virus vaccines, similar point estimates with widely overlapping CIs were found for the two vaccine types for the majority of serological assessments[9, 10, 15], with the exception of one study which found a statistically significant difference (i.e. non-overlapping CIs) in GMFR favouring the split virus IIV for influenza B[10].

Overall, the quality of immunogenicity evidence was weak. The two studies that compared subunit and split virus IIVs directly were rated "poor" due to concerns related to the comparability of the two intervention groups[9, 11]. Of the other three immunogenicity studies, one

was rated "fair", as there were concerns with response rate and comparability between the intervention groups[10], one was not evaluable, as it did not provide enough detail (i.e. methods were presented in a conference abstract)[15], and one study was not evaluable, as it did not report the design and there was no way to discern the design from the information provided[9].

Another limitation of the included immunogenicity studies is that all studies assessed immunogenicity by hemagglutination inhibition assay (HAI). These assays assess antibody as opposed to cell-mediated response, of which the latter has been shown to be a more robust correlation of protection in older adults[18]. Additionally, it is anticipated that results from HAIs would be similar for unadjuvanted, standard dose subunit and split virus IIVs, as the amount of HA antigen within these influenza vaccines is standardized. Therefore, HA antibody titres may not be an appropriate measure of immunogenicity to answer this research question.

IV.2 Review limitations

For this literature review, a rapid review of the evidence was completed rather than a full systematic review. Rapid reviews are increasingly being used to evaluate and synthesize evidence quickly; however, methodological standards for their conduct have not yet been established, and the term "rapid review" may be used to encompass a wide variety of disparate methods[19]. While the literature review was initially designed using a more restrictive rapid review protocol (i.e. limiting the number of electronic databases searched, limiting the year of publication, and no planned hand searching of the reference lists from included studies), post-hoc protocol modifications were made that were more consistent with a traditional systematic review (i.e. an unrestricted date range search of 6 electronic databases, and hand searching of the reference lists of all included studies) due to the low number of records retrieved from the initial search. Consistent with other rapid reviews[20], however, only one reviewer screened the retrieved articles for eligibility, and data extraction and quality assessments were performed by one reviewer and validated by a second.

The outcomes of using a rapid review methodology compared to a systematic review methodology have not yet been fully explored[21]. A scoping review conducted by Tricco et al. (2015) identified four studies that compared the results obtained from rapid reviews and full systematic reviews on the same topic[20]. Of a combined 17 rapid reviews identified in the four studies, only two reached conclusions that differed from those drawn from a full systematic review[22-25]. However, comparability of rapid and systematic reviews likely differs depending on the rapid review methodology employed. For this review, it is unlikely studies that directly compared subunit and split virus IIVs as a primary outcome were not retrieved. This is because all pivotal studies identified through hand searching, which had been excluded due to publication prior to 2007, were later retrieved by the modified search. However, these studies may have been erroneously excluded during the screening process, as Edwards et al. (2002) found that study selection involving only one reviewer missed an average of 8% of eligible studies compared to study selection involving two reviewers[26]. The impact this would have on the conclusions drawn from a rapid review are still unclear.

It is possible that the literature search may not have retrieved studies that examined VE against influenza by vaccine type in sub-analyses or as a secondary outcome. Broadening the search strategy to retrieve any study that reported VE estimates for influenza vaccines would have significantly increased the time required for screening. Despite this limitation, an advantage of the post-hoc modifications to the rapid review methodology is that hand searching the reference lists of included articles would likely mitigate the number of eligible articles of this type that may have been excluded by the search criteria.

Another limitation of this review is that many of the included studies defined older adults as participants who were ≥60 years of age. The inclusion of adults 60 to 64 years of age could affect the estimates for VE and immunogenicity and may lead to greater healthy vaccinee bias, as adults in this age range may be healthier than adults ≥65 years of age. Therefore, estimates from these studies should be interpreted with caution in the Canadian context, where older individuals are commonly defined as adults ≥65 years of age.

V. CONCLUSIONS

NACI concludes that there is insufficient evidence to determine significant differences in the VE or immunogenicity of unadjuvanted, standard dose subunit and split virus IIVs in adults 65 years of age and older (Grade I Evidence). The evidence available at this time is inconsistent and is not sufficient in quantity or quality to make specific recommendations on the differential use of unadjuvanted, standard-dose subunit and split virus IIVs in older adults.

LIST OF ABBREVIATIONS

Abbreviation	***Term***
aVE	Adjusted vaccine effectiveness
CCT	Clinical controlled trial
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
GMFR	Geometric mean fold rise
GMT	Geometric mean titre
HA	Hemagglutinin
HAI	Hemagglutination inhibition assay
IIV	Inactivated influenza vaccine
I-MOVE	Influenza Monitoring Vaccine Effectiveness in Europe
LAIV	Live attenuated influenza vaccine
NACI	National Advisory Committee on Immunization
PHAC	Public Health Agency of Canada
QIV	Quadrivalent inactivated influenza vaccine
RCT	Randomized controlled trial
TIV	Trivalent inactivated influenza vaccine
VE	Vaccine effectiveness

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Appendix A: Search strategy and results

OvidMEDLINE

Database(s): **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)**

#	Searches	Results
1	influenza vaccines/ or influenza, human/pc	26,064
2	(influenza, human/ or exp influenzavirus a/ or exp influenzavirus b/) and exp vaccines/	16,991
3	((flu or influenza* or h?n?) and (vaccin* or immuni?ation*)).tw,kf.	40,644
4	1 or 2 or 3	48,078
5	vaccines, subunit/	2,847
6	(subunit* or peptide*).tw,kf.	745,214
7	5 or 6	745,911
8	split*.tw,kf.	83,961
9	4 and 7 and 8	167
10	limit 9 to ("all aged (65 and over)" or "aged (80 and over)")	39
11	9 and (senior* or older adult* or geriatric or retired or retiree* or elder* or pensioner* or nursing home* or (("65 years" or "sixty five years") adj3 older)).tw,kf.	39
12	9 and (exp nursing homes/ or homes for the aged/ or exp aged/ or health services for the aged/)	39
13	10 or 11 or 12	50
14	limit 13 to (English or French)	44

Embase

Database(s): **Embase** 1974 to 2017 October 12

#	Searches	Results
1	influenza vaccine/ or influenza vaccination/ or exp influenza/pc or exp influenza virus/pc	41,924
2	(exp influenza/ or exp influenza virus/) and (vaccine/ or virus vaccine/ or inactivated virus vaccine/ or vaccination/)	12,802
3	((flu or influenza* or h?n?) and (vaccin* or immuni?ation*)).tw,kw.	48,064
4	1 or 2 or 3	65,137
5	subunit vaccine/ or peptide vaccine/	5,074
6	(subunit* or peptide*).tw,kw.	828,875
7	5 or 6	830,544
8	split*.tw,kw.	86,399
9	4 and 7 and 8	133
10	limit 9 to aged <65+ years>	22
11	9 and (senior* or older adult* or geriatric or retired or retiree* or elder* or pensioner* or nursing home* or (("65 years" or "sixty five years") adj3 older)).tw,kw.	28
12	9 and (nursing home/ or exp elderly care/ or exp aged/)	23
13	10 or 11 or 12	32
14	limit 13 to (English or French)	29

Cochrane Central Register of Controlled Trials
Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** September 2017

#	Searches	Results
1	influenza vaccines/ or influenza, human/pc	1,399
2	(influenza, human/ or exp influenzavirus a/ or exp influenzavirus b/) and exp vaccines/	1,068
3	((flu or influenza* or h?n?) and (vaccin* or immuni?ation*)).tw,kw.	3,155
4	1 or 2 or 3	3,243
5	vaccines, subunit/	118
6	(subunit* or peptide*).tw,kw.	12,227
7	5 or 6	12,257
8	split*.tw,kw.	4,719
9	4 and 7 and 8	37
10	9 and (senior* or older adult* or geriatric or retired or retiree* or elder* or pensioner* or nursing home* or (("65 years" or "sixty five years") adj3 older)).tw,kw.	13
11	9 and (exp nursing homes/ or homes for the aged/ or exp aged/ or health services for the aged/)	11
12	10 or 11	15

Web of Science
Database(s): **SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED**

#	Searches	Results
1	TS=((flu OR influenza*) AND (vaccin* OR immunis* OR immuniz*))	22,447
2	TS=((subunit* OR peptide*) AND split*)	1,393
3	TS=(senior* OR "older adult*" OR geriatric* OR retired OR retiree* OR elder* OR pensioner* OR "nursing home")	240,995
4	TS=(("65 years" OR "sixty five years") NEAR/3 older)	9,319
5	#1 AND #2 AND (#3 OR #4)	15

SCOPUS

(TITLE-ABS-KEY (((flu OR influenza* OR h?n?) AND (vaccin* OR immunis* OR immuniz*)))) AND (TITLE-ABS-KEY ((subunit* OR peptide*) AND split*)) AND ((TITLE-ABS-KEY (senior* OR older AND adult* OR geriatric OR retired OR retiree* OR elder* OR pensioner* OR nursing AND home)) OR (TITLE-ABS-KEY (("65 years" OR "sixty five years") W/3 older)))

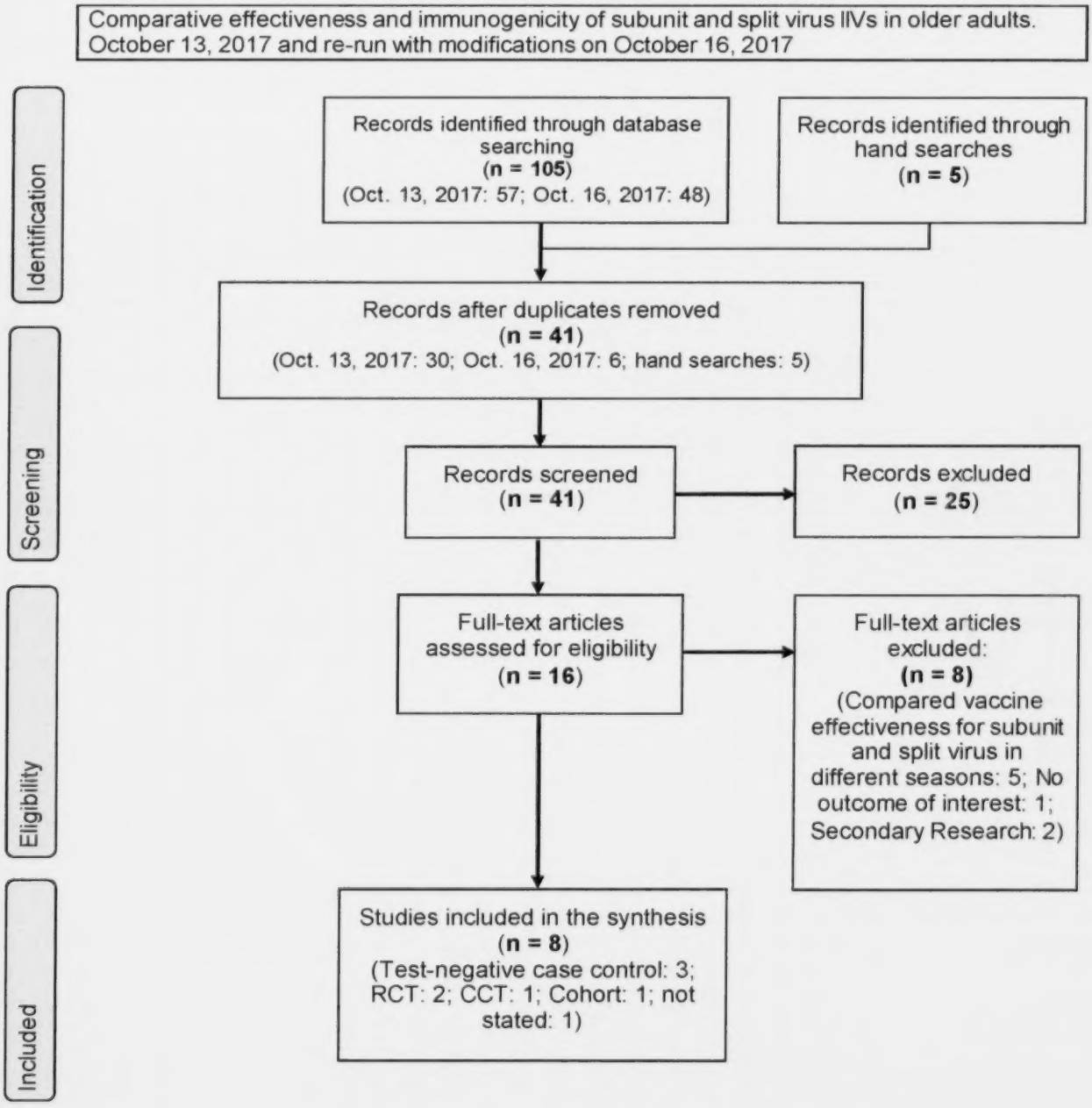
2 results

ClinicalTrials.gov

Your search:
((vaccin* OR immuni?ation*) AND (subunit* OR peptide*) AND split*)

0 results

Appendix B: Flow diagram


Comparative effectiveness and immunogenicity of subunit and split virus IIVs in older adults. October 13, 2017 and re-run with modifications on October 16, 2017
Identification
Screening
Eligibility
Included
Records identified through database searching (n = 105) (Oct. 13, 2017: 57; Oct. 16, 2017: 48)
Records identified through hand searches (n = 5)
Records after duplicates removed (n = 41) (Oct. 13, 2017: 30; Oct. 16, 2017: 6; hand searches: 5)
Records screened (n = 41)
Records excluded (n = 25)
Full-text articles assessed for eligibility (n = 16)
Full-text articles excluded: (n = 8) (Compared vaccine effectiveness for subunit and split virus in different seasons: 5; No outcome of interest: 1; Secondary Research: 2)
Studies included in the synthesis (n = 8) (Test-negative case control: 3; RCT: 2; CCT: 1; Cohort: 1; not stated: 1)

Appendix C: Level of evidence based on research design and quality (internal validity) rating of evidence

Table 1. Levels of Evidence Based on Research Design

LEVEL	DESCRIPTION
I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case–control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table 2. Definition of overall study quality

QUALITY RATING	DESCRIPTION
Good	A study (including meta-analyses or systematic reviews) that meets all design-specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

*General design specific criteria are outlined in Harris et al., 2001 [7]

Appendix D: Characteristics of influenza vaccines available for use in Canada, 2018–2019*

Manufacturer and Product Name	BGP Pharma ULC (Mylan) **Influvac®**	GlaxoSmithKline **Fluviral®**	Seqirus **Agriflu®**	Seqirus **Fluad Pediatric®** *and* **Fluad®**	Sanofi Pasteur **Fluzone® High-Dose**	AstraZeneca **FluMist® Quadrivalent**	GlaxoSmithKline **Flulaval® Tetra**	Sanofi Pasteur **Fluzone® Quadrivalent**
Vaccine Preparation	TIV	TIV	TIV	TIV	TIV	Live attenuated influenza vaccine (LAIV)	QIV	QIV
Vaccine Type	Inactivated (Surface antigen subunit)	Inactivated (Split virus)	Inactivated (Subunit)	Inactivated (Subunit)	Inactivated (Split virus)	Live attenuated	Inactivated (Split virus)	Inactivated (Split virus)
Route of Administration	Intramuscular (IM)	IM	IM	IM	IM	Intranasal spray	IM	IM
Authorized Ages for Use	3 years and older	6 months and older	6 months and older	Pediatric: 6–23 months Adult: 65 years and older	65 years and older	2–59 years	6 months and older	6 months and older
Antigen Content (Each of Strains)	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	Pediatric: 7 µg HA /0.25 mL dose Adult: 15 µg HA /0.5 mL dose	60 µg HA /0.5 mL dose	$10^{7.0-7.5}$ focus forming units of live attenuated reassortants /0.2 mL dose (Given as 0.1 mL in each nostril)	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose
Adjuvant	No	No	No	MF59 (Oil-in-water emulsion)	No	No	No	No
Formats Available	Single dose pre-filled syringes with luer tip	5 mL multi-dose vial	5 mL multi-dose vial, single dose pre-filled syringes without a needle	Single dose pre-filled syringes without a needle	Single dose pre-filled syringes	Prefilled single use glass sprayer	5 mL multi-dose vial	5 mL multi-dose vial, single dose vials, single-dose pre-filled syringes without attached needle
Post-Puncture Shelf Life for Multi-Dose Vials	Not applicable	28 days	28 days	Not applicable	Not applicable	Not applicable	28 days	Up to expiry date indicated on vial label
Thimerosal	No	Yes	Yes (Multi-dose vials only)	No	No	No	Yes	Yes (Multi-dose vials only)

Manufacturer and Product Name	**BGP Pharma ULC (Mylan)** **Influvac®**	**GlaxoSmithKline** **Fluviral®**	**Seqirus** **Agriflu®**	**Seqirus** **Fluad Pediatric®** *and* **Fluad®**	**Sanofi Pasteur** **Fluzone® High-Dose**	**AstraZeneca** **FluMist® Quadrivalent**	**GlaxoSmithKline** **Fulaval® Tetra**	**Sanofi Pasteur** **Fluzone® Quadrivalent**
Antibiotics (Traces)	Gentamicin	None	Kanamycin Neomycin	Kanamycin Neomycin	None	Gentamicin	None	None
Other Clinically Relevant Non-Medicinal Ingredients*	Egg protein Chicken protein Formaldehyde CTAB Polysorbate 80	Egg protein α-tocopheryl hydrogen succinate Polysorbate 80 Formaldehyde Ethanol Sodium deoxycholate Sucrose	Egg protein Formaldehyde Polysorbate 80 CTAB	Egg protein Formaldehyde Polysorbate 80 CTAB	Formaldehyde Egg protein Triton X-100	Egg protein Gelatin hydrosylate Sucrose Arginine Monosodium glutamate	Egg protein α-tocopheryl hydrogen succinate Polysorbate 80 Formaldehyde Ethanol Sodium deoxycholate Sucrose	Egg protein Formaldehyde Triton X-100 Sucrose

* Full details of the composition of each vaccine authorized for use in Canada and a brief description of its manufacturing process can be found in the product monograph.

** Refer to product monograph for alternate route(s) of administration.

Appendix E: Summary of evidence related to comparative effectiveness

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Kissling et al., 2014[12]	Subunit: Egg-based TIV Split virus: Egg-based TIV	Test-negative case-control (multicentre) Location: France Germany Ireland Poland Portugal Romania Spain Influenza season: 2012-2013 Funding: Co-funded by Sanofi Pasteur, Sanofi Pasteur MSD, GlaxoSmithKline EpiConcept, and the study sites	Population definition: Adults aged ≥60 years (stratified analysis) who presented to a participating clinic with influenza-like illness (sudden onset of at least one of: fever/feverishness, malaise, headache, or myalgia AND at least one of: cough, sore throat, or shortness of breath) or acute respiratory illness (France and Germany) symptoms. Have been swabbed within 7 days of onset, no contraindications to influenza vaccine, & did not receive antivirals prior to swabbing. Sample size: Total: 6,634 ≥60 years: 419 ≥60 years and subunit: 39 ≥60 years and split: 82 Age: Mean (Range): Not reported Sex (% female):	aVE against infection with any laboratory-confirmed influenza strain: Description: VE against laboratory-confirmed influenza adjusted by covariates in 60 years of age and older Finding: Subunit: 64.6 (95% CI: 21.6-84.0) Split virus: 54.1 (95% CI: 16.8-74.7) Adjusted for onset week, presence of at least one chronic condition (including pregnancy and obesity if available), age, and sex.	Level II-2	Fair VE is not adjusted by geographic location or study site

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
			Not reported for age range of interest Total controls: 51% Total A(H1N1): 53% Total A(H3N2): 49% Total B: 50%			
Rondy et al., 2017[14]	Subunit: Inactivated (TIV) Split virus: Inactivated (TIV)	Test-negative case-control (multicentre) Location: France Poland Portugal Romania Spain Croatia Finland Hungary Lithuania the Netherlands Italy Influenza season: 2015-2016 Funding: Grants from the European Union's Horizon 2020 research and innovation programme and the Research Council of Lithuania	Population definition: Community dwelling adults ≥65 years of age admitted to hospital for clinical conditions possibly related to influenza and who met definition for severe respiratory infection in last 7 days (hospitalized AND at least one systemic symptom of: fever/feverishness, malaise, headache, or myalgia AND at least one of: cough, sore throat, or shortness of breath at admission or within 48hrs after admission). Patients had no contraindications for influenza vaccination or previous laboratory-confirmed influenza in the season of study. Sample size: Total: 1802 Subunit: 338 Split: 513 Subunit (H1N1	aVE against laboratory-confirmed influenza hospitalization: Description: VE against hospitalized influenza adjusted by covariates Finding: H1N1: Subunit: 28.1 (95% CI: -8.6, 52.4) Split virus: 54.7 (95% CI: 30.7, 70.4) B: Subunit: 49.0 (95% CI: 13.5-70.0) Split virus: 54.1 (95% CI: 18.9-74.0) Adjusted for study site, date of onset, and age.	Level II-2	Fair VE is not adjusted by sex, chronic condition, or hospitalization in previous year. Potential for residual confounding by study site, given that nearly half of study locations only administered one type of influenza vaccine Proportion of participants who had specimen collection within 3 days of onset differed statistically significantly between cases and controls

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
			analysis): 286 Split (H1N1 analysis): 371 Subunit (B analysis): 227 Split (B analysis): 362 Age: Median. A(H1N1) cases: 76 A(H1N1) controls: 78 B cases: 76 B controls: 78 Range: 65-101 Sex (% female): A(H1N1) cases: 44.7% A(H1N1) controls: 47.5% B cases: 48.2% B controls: 48.7%			
Talbot et al., 2015[13]	Subunit: Agriflu and Fluvirin Split virus: Afluria, Fluarix, FluLaval, and Fluzone Standard Dose	Test-negative case-control (multicentre) Location: United States Influenza season: 2008-2009 2010-2011 2011-2012 Funding: Grants from the United States Centers for Disease Control and Prevention, RTI International,	Population definition: Adults aged ≥50 years seeking medical care for acute respiratory illness or fever without other known non-respiratory causes; sub-analyses conducted for adults ≥65 and ≥70 years Sample size: Not reported for ≥65 Total: 539 Subunit (total): 150 Split (total): 204 Age (total): Median:	aVE against infection with any laboratory-confirmed influenza strain: Description: Difference in adjusted VE (split - subunit) Finding: 65 or older: 41.9 (95% CI: -5.5, 190.6) 70 or older: 62.4 (95% CI: -112.4, 555.1) All findings adjusted for age in years, sex, race (black vs. nonblack), current smoking (past 6 months), underlying medical conditions (diabetes, chronic heart/kidney disease, cardiovascular disease, asthma, chronic obstructive pulmonary disease, asplenia), immunosuppression (HIV, corticorsteroid use, or cancer), influenza season, timing relative to onset of flu season,	Level II-2	Fair High proportion (36%) of enrolled participants excluded due to missing data

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		and the National Institutes of Health	Subunit: 69.4 Split: 67.5 Sex (% female) (total): Subunit: 56% Split: 62%	enrollment site (ED, inpatient, outpatient)		

Appendix F: Summary of evidence related to comparative immunogenicity

STUDY DETAILS						
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Morales et al., 2003[10]	Subunit: Agrippal S1 Split virus: Imovax Gripe	RCT (multicentre) Location: Colombia Influenza season: 1999-2000 (Nov-Dec) Funding: Not stated	Population definition: Healthy and status compatible with vaccination (e.g. not previously vaccinated in season of study) adults aged ≥60 years (stratified analysis, full study included adults ≥18 years) Sample size: Total: 341 ≥60: 140 Subunit (≥60): 66 Split (≥60): 74 Age (≥60): Mean (range): Subunit: 70.1 (60-89) Split: 70.3 (60-86) Sex (% female) (≥60): Subunit: 46% Split: 45%	Seroprotection rate: Description: % with HA titre ≥40 post-vaccination. Finding: Subunit (range for all strains): 88-98 Split: (range for all strains): 88-97 GMFR: Description: GMFR of HA antibodies ratio of post- to pre-vaccination GMT of HA antibodies Finding: Subunit (A(H1N1)): 14.4 (95% CI: 10.0-20.7) Split (A(H1N1)): 16.8 (95% CI:11.5-24.4) Subunit (A(H3N2)): 10.9 (95% CI: 7.6-15.8) Split (A(H3N2)): 10.9 (95% CI: 7.6-15.7) Subunit (B): 4.1 (95% CI: 3.1-5.3) Split (B): 9.3 (95% CI: 7.0-12.34) Seroconversion rate: First Description: % with HA titre increase from <10 pre-vaccination to ≥40 post-vaccination Finding: Subunit (A(H1N1)): 81 Split (A(H1N1)): 86 Subunit (A(H3N2)): 88 Split (A(H3N2)): 86	Level I	Fair Conducted a per-protocol analysis and did not detail losses to follow up, or analyze participant characteristics between study groups

STUDY DETAILS						
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				Subunit (B): 67 Split (B): 89 Second Description: % with pre-vaccination titer ≥10 and at least a four-fold rise post-vaccination Finding: Subunit (A(H1N1)): 79 (95% CI: 58-93) Split (A(H1N1)): 55 (95% CI: 32-77) Subunit (A(H3N2)): 72 (95% CI: 59-83) Split (A(H3N2)): 75 (95% CI: 63-84) Subunit (B): 54 (95% CI: 40-67) Split (B): 71 (95% CI: 58-83)		
Skowronski et al., 2012[15]	Subunit: Agriflu Split virus: Vaxigrip	RCT (multicentre) Location: Canada Influenza season: 2011-2012 Funding: Co-funded by Michael Smith Foundation for Health Research, the institutes of the investigators, and a grant from the Canadian Institutes of Health Research. Novartis and Sanofi Pasteur contributed	Population definition: Adults aged ≥65 years who received at least 1 dose of seasonal TIV within the previous 2 years Sample size: Total: 182 Subunit: 79 Split: 31 Age: Median (range): Subunit: 73 (65-83) Split: 74 (65-84) Sex (% female): Not reported	GMFR (for A(H3N2v), emerging swine-origin variant - A/Indiana/10/2011): Description: geometric mean titre rise of HA antibodies (ratio of post-vaccination GMT/pre-vaccination GMT) Finding: Subunit: 1.13 Split virus: 1.51 Seroprotection (for A(H3N2v), emerging swine-origin variant - A/Indiana/10/2011): Description: % with HA titre ≥40 Finding: Subunit: 27 (95% CI: 17-37) Split virus: 32 (95% CI: 15-50) Seroconversion (for A(H3N2v), emerging swine-origin variant - A/Indiana/10/2011):	Level I	N/A Insufficient information regarding study methods to assess quality

STUDY DETAILS

Study	Vaccine	Study Design	Participants	Summary of Key Findings	Level of Evidence	Quality
		funding to immunologic testing only		Description: % with 4-fold increase in HA titre or increase from <10 pre-vaccination to ≥40 post-vaccination Finding: Subunit: 0 (95% CI: not reported) Split virus: 7 (95% CI: 0-21)		
Zei et al., 1991[11]	Subunit: Isiflu Zonale 10ug per 0.5 ml Split virus: Vaxigrip 10ug per 0.5 ml	CCT Location: Italy Influenza season: 1989-1990 Funding: Not stated	Population definition: Adults aged ≥60 years (stratified analysis, full study included adults ≥17 years) Sample size: Total: 149 ≥60 years: 84 Subunit (≥60 years): 60 Split (≥60 years): 24 Age: Median (range): Subunit (≥60 years): 68 (61-83) Split (≥60 years): 70 (60-77) Sex (% female): Not reported	Seroprotection rate: Description: % with HA titre ≥40 Finding: Subunit (A(H1N1)): 46% Split (A(H1N1)): 71% p-value: <0.05 Subunit (A(H3N2)): 52% Split (A(H3N2)): 71% p-value: >0.05 Subunit (B): 3% Split (B): 42% p-value: >0.05 Seroconversion rate: Description: % with 4-fold increase in HA titre or increase from <10 pre-vaccination to ≥40 post-vaccination Finding: Subunit (A(H1N1)): 40% Split (A(H1N1)): 54% p-value: >0.05 Subunit (A(H3N2)): 17% Split (A(H3N2)): 37.5% p-value: <0.05	Level II-1	Poor Unclear how initial exposure groups were assembled; Losses to follow up not discussed; adjustment for potential confounders was not considered

STUDY DETAILS

Study	Vaccine	Study Design	Participants	Summary of Key Findings	Level of Evidence	Quality
				Subunit (B): 5% Split (B): 50% p-value: <0.001		
Camilloni et al., 2016[8]	Subunit: Not stated 1988-1989 to 1991-1992: 10 ug /antigen 1992-1993 and later:15ug/antigen Split virus: Not stated 1998-1989 to 1991-1992: 10 ug/antigen 1992-1993 and later:15ug/antigen	Cohort (multicentre) Location: Italy Influenza season: 1988-1989 to 2014-2015 (27 consecutive seasons; however split/subunit vaccines were not administered every year) Funding: Not stated	Population definition: Adults aged ≥60 years who resided in a nursing home and vaccinated with that season's commercially available seasonal TIV. In 1988-1999 both community and nursing home adults were recruited Sample size: Total: 4461 Subunit: 1094 Split: 996 Age: Mean (range): 85 (60-106) Sex (% female): 70%	GMFR: Description: GMFR (Ratio of post- to pre-vaccination GMT)of split compared to subunit vaccine Finding: A(H1N1): Split virus significantly lower than subunit vaccine (p<0.01) A(H3N2): not significantly different (p>0.05) B: not significantly different (p>0.05) Seroprotection: Description: % volunteers showing HA titers ≥40 for split compared to subunit vaccine Finding: A(H1N1): Split virus significantly lower than subunit vaccine (p<0.01) A(H3N2): not significantly different (p>0.05) B: Split virus significantly higher than subunit vaccine (p<0.01) Seroconversion: Description: % subjects with a fourfold or greater increase in titer and with a post-vaccination titer ≥40 in seronegative volunteers for split compared to subunit vaccine Finding: A(H1N1): Split virus significantly lower than subunit vaccine (p<0.01) A(H3N2): not significantly different (p>0.05)	Level II-2	Poor Did not adjust for potential confounders; did not discuss initial differences in cohort assembly; different doses of vaccine compared over time

STUDY DETAILS						
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				B: not significantly different (p>0.05)		
Del Giudice et al., 2006[9]	Subunit: Agrippal Split virus: Begrivac	Design not stated Location: Not stated Influenza season: 2003-2004 Funding: Not stated	Population definition: Older adults who received a single dose of seasonal TIV Sample size: Total: 119 Subunit: 29 Split: 30 Age: Range: 61-91 Sex (% female): 47%	Seroprotection rate: Description: % with HA titre ≥40 Finding: Subunit [A(H3N2) vaccine strain]: 96.5 Split [A(H3N2) vaccine strain]: 96.7 Subunit [A(H3N2) mismatched circulating strain]: 75.9 Split [A(H3N2)]mismatched circulating strain): 80	N/A (III)	N/A Quality was not assessed because study design could not be determined